placebo in patients with systemic lupus erythematosus, few studies renewed interest for this molecule.

We hypothesised that applying new SLE response criteria in EXPLORER study, we could show rituximab efficacy. Our objective was to reanalyze EXPLORER trial's data using four newly described SLE response criteria.

Methods In our reanalysis, rituximab efficacy was assessed at week 52 using 4 criteria: SRI-4 (Systemic lupus erythematosus Responder Index) with and without a concomitant oral corticosteroid tapering objective of <10 mg at months 6 (SRI-4 with or without OCS tapering), Lupus Low Disease Activity Score (LLDAS) and BILAG-based Combined Lupus Assessment (BICLA).

Results Data from all 257 patients were available. There was 234 women (91%) with a mean age of 40, 3 years among which 177 (69%) received hydroxychloroquine.

At week 52, SRI-4 response rate was 27,2% in the rituximab group vs 22,7% in the placebo group ($p=0.43$); SRI-4 with OCS tapering was 16% in the rituximab group vs 13.6% in the placebo group ($p=0.62$); LLDAS was 16% in the rituximab group vs 12.5% in the placebo group ($p=0.46$) and BICLA was 15.4% in the rituximab group vs 15.9% in the placebo group ($p=0.91$).

Subgroup analyses demonstrated a trend for better efficacy of rituximab compared to placebo in the subgroup of patients co-treated with methotrexate: SRI-4 of 30.6% in the rituximab group vs 12% in the placebo group ($n=74$, $p=0.08$). This trend was not found in the subgroup of patients co-treated with azathioprine or mycophenolate. In the subgroup of patients with an BILAG A/B in haematological system or vasculitis at baseline, there was a significantly higher SRI-4 response rate with rituximab: 28,6% vs 5,3% in the haematological group ($p=0.047$) and 39,3% vs 0% in the vasculitis group ($p=0.037$).

Conclusions Our study confirms the results from the original EXPLORER Study. However, subgroup analysis suggests that patients with haematological or vasculitis involvement might benefit from rituximab. Efficacy in the subgroup treated with methotrexate is likely to be due to a lesser bias of concomitant immunosuppressive medication compared to azathioprine and mycophenolate.

S6d – Immunopathogenesis II

S6D:4 ANTIBODIES TO MYELIN OLIGODENDROCYTE GLYCOPROTEIN IN PATIENTS WITH SLE ARE ASSOCIATED WITH CENTRAL NERVOUS SYSTEM INVOLVEMENT: AN UNBIASED PILOT STUDY OF THE SWISS SLE COHORT STUDY (SSCS)

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Background Nervous system involvement in systemic lupus erythematosus (SLE) is mediated either through autoimmune

vascular or inflammatory processes. The aetiology leading to inflammatory processes to date remains largely elusive. Given that the pathophysiologic hallmark of SLE is B cell hyperactivity, we hypothesised that antibodies against components of the central and peripheral nervous system might be present in the serum and contribute to inflammation/demyelination in these patients.

Purpose To determine the prevalence of a broad panel of novel and known nervous system (NS)-directed antibodies in a large, unbiased cohort of patients with systemic lupus erythematosus (SLE) in the Swiss Lupus Erythematosus Cohort Study (SSCS).

Methods This retrospective pilot study included 174 patients in a cross-sectional analysis and 104 patients in a longitudinal study. Antibodies against 12 NS-antigens (myelin oligodendrocyte glycoprotein (MOG), neurofascin 186 (NF186), aquaporin-4 (AQP4), N-methyl-D-aspartate receptor (NMDAR), AMPA-receptor subunit 1 and 2 (AMPA), gamma-aminobutyric acid B receptor (GABABR), Glycine-receptor (GlyR), metabolic glutamate receptor 5 (mGluR5), glutamate decarboxylase 65 (GAD65), voltage-gated potassium channel (VGKC)-complex antibodies (contactin-associated protein-like 2 (CASPR2), Leucine-rich glioma inactivated 1 (LGI1)), and dipeptidyl-peptidase-like protein 6 (DPPX) were screened with cell-based assays and correlated with clinical and diagnostic findings.

Results 23/174 patients harboured antibodies against MOG ($n=14$), NF186 ($n=6$), GAD65 ($n=2$), AQP4 and GlyR ($n=1$), of which 13 showed clinical symptoms of NS involvement that resembled the syndrome associated with the antibody. Nine patients harbouring antibodies have remained clinically asymptomatic to date, while another patient was lost to follow-up. Antibodies against MOG were those found most frequently (8%) and their titer correlated with the severity of neurologic involvement. The frequency of neuropsychiatric SLE (NPSLE) was much higher in the NS-antibody-positive patients (43%, 83%, 100%, 0% versus 14%).

Conclusions Antibodies against MOG, NF186, GAD65, AQP4 and GlyR are found in patients with SLE and NS involvement, of which MOG-antibodies are the most prevalent. This is the first large, unbiased study to screen for a broad panel of anti-NS antibodies. Screening for these antibodies could serve as a predictor and biomarker for inflammatory NS involvement in NPSLE and potentially aid in tailored treatment decisions.

S6D:5 ANTIPHOSPHOLIPID ANTIBODIES DIFFERENTIALLY REGULATE THE EXPRESSION & ACTIVITY OF THE LYSOSOMAL PROTEASES WITH EFFECTS UPON MONOCYTE AUTOPHAGY

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Purpose Antiphospholipid antibodies (aPL) activate monocytes in antiphospholipid syndrome (APS), although the precise mechanisms by which this activation occurs are not fully understood. We have identified several novel protein targets using proteomic analysis of human monocytes treated with APS-IgG. Amongst these novel targets lysosomal proteases cathepsin B and D were identified. The balance between different cathepsins is important in protein degradation,

apoptosis and autophagy. Reduced cathepsin B and D with increased cathepsin L is a phenotype suggesting reduced autophagy. Dysregulation of autophagy may be important in the pathogenesis of APS. Therefore, we aimed to determine the effect of aPL on monocyte cathepsin balance and autophagy.

Methods Healthy control (HC) monocytes were treated with 200 µg/ml of IgG purified from (n=9) patients with APS-IgG or (n=9) HC-IgG for 6 hour. Cathepsin B and D expression were measured by western blot. Cathepsin D, B and L activity were measured using fluorescence-based assays. Intracellular proteolytic activity was determined using DQ-BSA.

Results Consistent with our previous proteomic analysis, western blots confirmed that cathepsin B and cathepsin D were down-regulated in monocytes treated with APS-IgG compared to HC-IgG. Similarly, cathepsin B and D activities were significantly reduced in monocytes treated with APS-IgG ($p=0.0188$ for B, 0.0323 for D). In contrast, cathepsin L activity was increased in monocytes treated with APS-IgG ($p=0.0106$). We then examined cathepsin activity in monocytes from patients with APS. Cathepsin L activity was increased significantly when these monocytes were treated with APS-IgG compared to HC-IgG ($p=0.0257$).

Lysosomal proteolysis is a key process in the late phase of autophagy. We therefore exposed HC monocytes to IgG, treated them with GM-CSF overnight and tested their intracellular proteolytic activity. APS-IgG reduced the lysosomal activity of GM-CSF-treated monocytes whereas HC-IgG had no effect.

Conclusions We found that APS-IgG regulate the expression and activity of lysosomal proteases cathepsins B/D and cathepsin L in opposite directions. Consistent with this finding, APS-IgG reduced lysosomal proteolysis in monocytes. Additional experiments are now underway to increase our understanding of how modulation of cathepsin activity and autophagy may be important in the pathogenesis of APS and to provide new therapeutic targets.

S6D:6 INHIBITION OF EIF4A TRANSLATION INITIATION AMELIORATES LUPUS MANIFESTATIONS

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Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterised by loss of tolerance and presence of auto reactive B and T cells. Pathogenic mechanisms of the disease are still unclear and clinical manifestations are heterogeneous complicating diagnosis and disease treatment. Several organs can be affected such as skin, joints, central nervous system, and kidneys. Current treatments include corticosteroids and immunosuppressive drugs, nonsteroidal anti-inflammatory drugs, antimalarials and other biologicals such as belimumab or rituximab. During the last decades mouse models have been very helpful to understand lupus pathogenesis and to test the efficacy of SLE therapies. In this work we evaluated the

therapeutic potential of inhibiting the translation initiation process with Pateamine A, a natural compound isolated from a marine sponge, in a lupus preclinical model. Translation initiation via the eIF4E complex is a key step in cytokine and antibody production, and its inhibition has been successful in cancer models. Pateamine A has anti-proliferative and immunosuppressive activities. In the BXSB.Yaa strain, we tested the efficiency of Pateamine A in controlling lupus autoimmune symptoms and neurological complications. Animal treatment started when first signs of disease were present (12 weeks) and finished at the time in which the strain has a mortality rate of 50% (5 months). Our data shows that Pat A treatment reduces circulating levels of proinflammatory cytokines and autoantibodies increasing survival. An improvement in cognitive functions in treated animals was also observed with neural behaviour tests (learning/memory, and depression) together with a reduction of proinflammatory cytokines in the hippocampus. We did not observe any side effects of the treatment. Altogether our data suggests that inhibition of translation initiation has an effect in controlling disease activity at the immunological and neurological levels and open a new line of research for strategies to treat lupus and other autoimmune diseases based on the inhibition of translation at early stages.

S6D:7 NOVEL ALPHA-1-ANTITRYPSIN FRAGMENT AS POTENTIAL TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by a loss of immunologic tolerance, production of auto-antibodies and inflammatory damage in multiple organs. We have tested the effect of a novel anti-inflammatory peptide, a fragment of alpha-1-antitrypsin, termed UBE on two animal models of SLE, MRL/lpr and NZBW/F1 mice. Treatment of MRL/lpr mice with low dose of UBE (1 microgram/kg) at early stage of disease namely, 12 weeks old mice, caused significant reduction in proteinuria and hematuria. The beneficial effect of the peptide was corroborated by histological examination. Furthermore, a significant reduction in serum IL17, IL12 and anti dsDNA antibodies was observed in the UBE-treated mice. Isolated CD4 cells incubated with the peptide showed similar cytokine profile. Decreased levels of double negative CD4-CD8- and B220+ cells were determined in lymph organs of UBE-treated animals. Similar effects were observed with NZBW/F1 mice, namely, the peptide (0.3 microgram/kg) caused significant reduction in proteinuria and, kidney and lung damage as determined in histopathological examination. The highly important SLE serum factor B-lymphocyte stimulator (BLyS or BAFF) was dramatically decreased in UBE-treated mice. Spleen and blood double negative CD4-CD8- and serum IL6, IP10 and MCP1 were significantly reduced in peptide-treated mice. The beneficial effects of UBE suggest this peptide as potential drug for SLE.